Cystadenomas of the Pancreas

Is Enucleation an Adequate Operation?

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Objective

The objective was to determine whether surgical enucleation of mucinous cystadenoma of the pancreas is a safe and adequate operation.

Summary Background Data

Mucinous cystadenomas of the pancreas are premalignant cystic lesions. Resection is the preferred treatment but often requires a pancreatoduodenectomy or a distal pancreatectomy with or without a splenectomy. Although these procedures can now be performed with a low mortality rate, substantial morbidity still occurs, especially in patients who have an otherwise normal pancreas.

Methods

Between January 1990 and June 1997, 36 mucinous cystadenomas of the pancreas were resected at The Johns Hopkins Hospital. Most of these patients underwent pancreatoduodenectomy or distal pancreatectomy. However, 10 patients (28%) underwent enucleation of their cystic tumor. These 10 patients had a mean age of 63 years, and 6 were men. The cystic lesion was demonstrated by computed tomography in all patients. Enucleation of the cyst was performed in each patient, and four underwent another concomitant abdominal procedure. These 10 patients were followed with periodic computed tomographic scans and clinical examinations.

Results

Enucleation took less time and was associated with less blood loss than resection. Pancreatic fistulas occurred more frequently after enucleation, but the incidence of major complications was similar between the two groups. Follow-up after enucleation averaged 43 months, and none of the patients developed late sequelae or recurrence.

Conclusions

This experience suggests that enucleation of mucinous cystadenomas of the pancreas can be performed safely and that the recurrence rate is low after this procedure. The authors conclude that enucleation is an adequate procedure for benign cystic neoplasms of the pancreas.

Cystic tumors of the pancreas are unusual lesions with a spectrum of aggressiveness. One classification system sorts these tumors into the following classes: type Ia serous cystadenoma, type Ib mucinous cystadenoma, type II mucinous cystadenocarcinoma, and type III adenocarcinoma with mucin production or an associated cyst.[1] These lesions can be easily clinically misidentified as benign cysts such as pseudocysts or simple pancreatic cysts. As a result, many experts routinely explore and resect these lesions. However, resection of an otherwise normal pancreas can be associated with morbidity, occasional death, and late sequelae.

Experience with benign lesions in other organs, such as hepatic cysts and hemangiomas, has demonstrated the feasibility of enucleation. Enucleation has the obvious advantage of preserving organ parenchyma, but it also may be a less risky and less time-consuming procedure. The simple encapsulated nature of pancreatic cystic type Ib tumors, benign mucinous cystadenomas, led us to consider whether safe and effective extirpation could be accomplished by simple enucleation as opposed to segmental organ resection. Therefore, enucleation of mucinous cystadenomas of the

Table 1. PATIENT AND TUMOR CHARACTERISTICS

	Resection	Enucleation
Number (% of total)	26 (72)	10 (28)
Age (range) (yr)	53 (23–81)	63 (24–75)
Female (%)	65	40
White (%)	77	70
Location		
Head (%)	23	30
Ucinate (%)	4	30
Body/tail (%)	73	40
Size (cm ± SEM)	3.6 ± 0.51	2.8 ± 0.61
<4 cm (%)	62	80
Volume (mL ± SEM)	71 ± 29	30 ± 18

pancreas was performed in a select group of patients over the past 7 years. This retrospective study compares a series of mucinous cystadenomas removed by simple enucleation to those removed by segmental pancreatic resection during the same period.

MATERIALS AND METHODS

Patient and Tumor Characteristics

Thirty-six patients who underwent surgery for removal of a mucinous cystadenoma of the pancreas between January 1990 and June 1997 were retrospectively reviewed. During this same period, 114 patients underwent surgery for a cystic lesion of the pancreas. Twenty-six of the 36 patients (72%) with mucinous cystadenomas underwent resection of their tumor by either distal pancreatectomy or pancreatoduodenectomy. The remaining 10 patients (28%) underwent enucleation of the mucinous cystadenoma. The patient characteristics of these two groups are summarized in Table 1. The average age of patients who underwent resection was 53 years (range, 23 to 81), and 17 were women (65%). Seven cystic tumors in this group were located in the head or uncinate process (27%), and 19 were in the body or tail (73%). The 10 patients whose tumors were enucleated had a mean age of 63 years (range, 24 to 75), and 4 were women (40%). All cysts in both groups were characterized before surgery by computed tomography (CT) scanning. Only 27%

Figure 1. Location and size of mucinous cystadenomas.

Table 2. PRESENTATION

	Resection	Enucleation
Pain (%)	60	20
Weight loss (%)	16	20
Nausea (%)	12	10
Asymptomatic (%)	8	30

of the resected lesions were in the head or uncinate process *versus* 60% of the enucleated cystadenomas (Fig. 1). On average, the resected cystadenomas were larger (3.63 cm; range, 0.5 to 11 cm.) than the enucleated cystadenomas (2.82 cm; range, 1 to 7 cm). Only 62% of the resected lesions were <4 cm in diameter *versus* 80% of the enucleated lesions (see Table 1). None of these differences achieved statistical significance.

Presentation

The major features of patient presentation are summarized in Table 2. Pain was present in 60% of patients who underwent resection *versus* 20% of those who underwent enucleation. The incidences of weight loss and nausea were similar. Only 2 (8%) of the resected patients had no symptoms at presentation (the tumor was discovered during studies for other conditions) *versus* 30% of the patients who underwent enucleation. Other presenting symptoms were present in <10% of either group.

Enucleation

Patients were considered to be candidates for enucleation if their preoperative and intraoperative evaluation strongly suggested a benign mucinous cystadenoma. Additional criteria were size of the cyst, absence of jaundice, and no vascular involvement on CT scan. At celiotomy, additional criteria for enucleation included an assessment that the entire cystic lesion could be resected by enucleation, and that no adjacent organs were involved. If these criteria could not be met, the lesion was resected. Figure 2 shows operative photographs of the enucleation of a mucinous cystadenoma from the uncinate process.

Operative Procedures

The operative procedures performed to remove the mucinous cystadenomas are summarized in Table 3. Nineteen of the 26 patients (73%) who were resected underwent distal pancreatectomy. Fourteen of the 19 distal pancreatectomy patients (74%) also had splenectomy. Thus, 54% of the resection group underwent splenectomy. One patient underwent distal pancreatectomy, splenectomy, and left adrenalectomy, and one patient underwent distal pancreatectomy and partial gastrectomy. Four of the 10 patients who under-
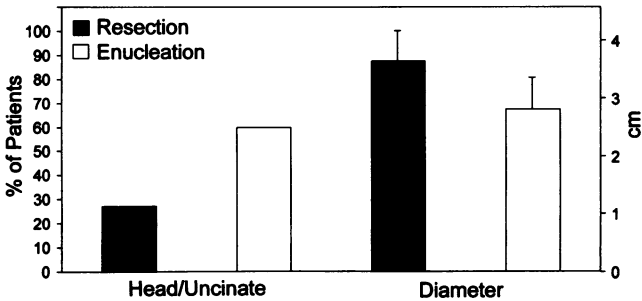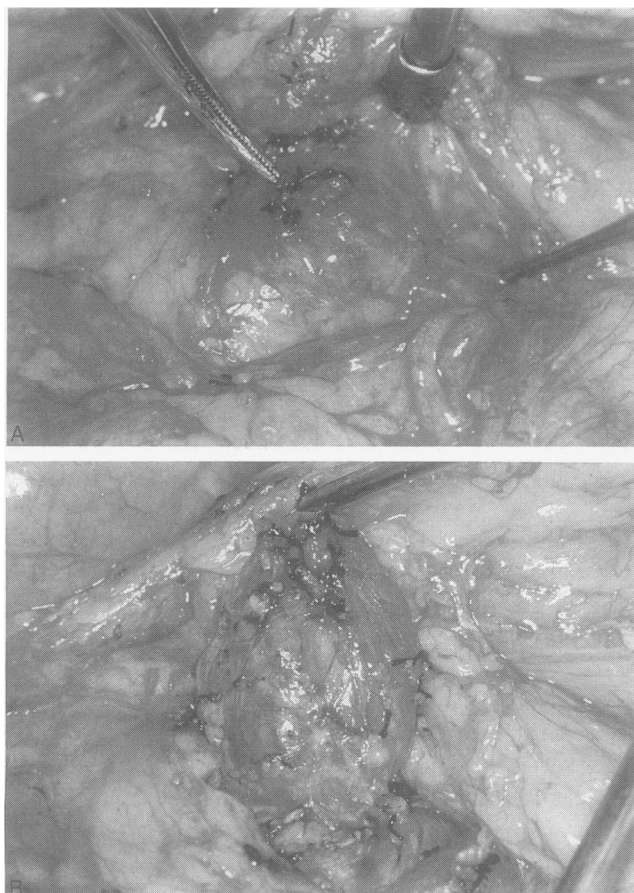
Figure 2. (A) Mucinous cystadenoma of the uncinate; the surgical clamp is pointing at the lesion. (B) Same tumor, nearly completely enucleated. The gallbladder is in the background and the superior mesenteric vein in the foreground.

went enucleation had a combined procedure. In one patient enucleation was combined with cholecystectomy, and in another it was combined with gastric fundoplication for reflux esophagitis. Another patient had combined enucleation and longitudinal pancreatojejunostomy. The final patient had a mucinous cystadenoma enucleated in the body of the pancreas combined with pancreatoduodenectomy for adenocarcinoma of the head of the pancreas. In this patient, enucleation avoided the need for total pancreatectomy. Octreotide was not routinely used in either the resection or the enucleation group. The average operative time was similar for resection and enucleation. However, the average blood loss with enucleation was less than with resection by 302 cc (p = 0.07).

Morbidity

Morbidity was stratified into pancreas-related and non-pancreas-related, and as major and minor. Pancreas-related complications included fistula, pseudocyst formation, and pancreatitis. A pancreatic fistula was defined as drainage of >50 ml of amylase-rich fluid (more than threefold elevation

higher than the upper limit of normal in serum) through the operatively placed drains on or after postoperative day 10, or pancreatic anastomotic disruption demonstrated radiographically.[2] Major complications included stroke, partial bowel obstruction, gastric outlet obstruction, adult respiratory distress syndrome, as well as any pancreas-related complication. Minor complications included wound infection and persistent nausea.

Follow-Up and Statistics

Follow-up and survival information was obtained from hospital medical records, the hospital computer system, and surgeon follow-up clinic visit notes. Statistical analysis was performed on all pertinent patient data. Comparisons were made between the resection group and the enucleation group using Student's t test and the Mann–Whitney rank sum test for continuous variables, as appropriate. Analysis of proportions between the two groups was performed using the chi square test. Statistical significance was achieved at p < 0.05.

RESULTS

Mortality and Morbidity Rates

No intraoperative deaths occurred, and no hospital deaths were observed among the 10 patients who underwent enucleation. Two deaths occurred in the resection group, one because of a cerebrovascular accident occurring late in the hospital course. The other patient developed sepsis after pancreatic anastomotic disruption. Patients who underwent enucleation had a significantly greater incidence of pancreatic fistula than did patients who underwent resection (50% vs. 12%, p < 0.05) (Fig. 3). All fistulas that occurred after enucleation resolved with conservative management, which led to an increased length of stay in the enucleation group versus the resection group (19.5 vs. 10 days, p < 0.02) (Table 4). Additional complications in the resection group included stroke (8%), gastric outlet obstruction (8%), adult

Table 3. PROCEDURES, OPERATIVE TIME, AND BLOOD LOSS

	Resection	Enucleation
Distal pancreatectomy (%)	73	
With splenectomy (%)	54	
Without splenectomy (%)	19	
Pancreatoduodenectomy (%)	27	
Enucleation		100
Alone (%)		60
With another procedure (%)		40
Operative time (min ± SEM)	313 ± 36	272 ± 42
Blood loss (ml ± SEM)	511 ± 111	209 ± 35*

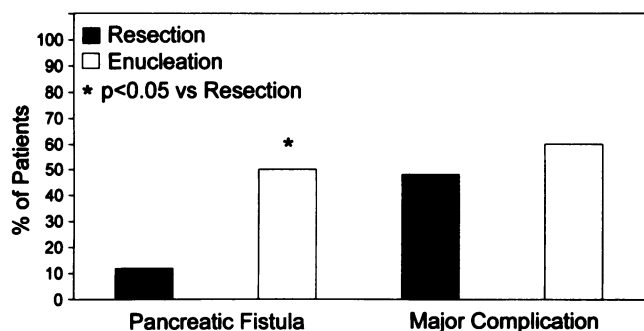* p = 0.07 vs. resection by Student's t test.

Figure 3. Postoperative morbidity.

respiratory distress syndrome (4%), pseudocyst formation (4%), partial small bowel obstruction (4%), and incisional hernia (4%). Other complications in the enucleation group included pancreatitis (10%), wound infection (10%), and abscess easily treated with drainage (10%). Ten percent of the resected patients required insulin after the procedure *versus* none of the enucleated patients. Although the fistula rate was higher in the enucleation group, the rate of major complications was similar in both groups (see Fig. 3).

Follow-Up

Data regarding follow-up are summarized in Table 4. Follow-up ranged from 4 to 110 months and averaged 48.6 months for the resected group and 42.9 months for the enucleation group. Based on follow-up CT information, no recurrences of mucinous cystadenoma occurred in the 10 patients who underwent enucleation. Figure 4 shows a preoperative CT of a mucinous cystadenoma in the body of the pancreas and a scan taken 7 years later showing no recurrence of the cystic lesion in the pancreatic bed. In addition to the two hospital deaths in the resection group, an additional patient, who had undergone distal pancreatectomy and splenectomy, died of viral pneumonia 16 months after surgery. Moreover, 10% of the resected patients developed late diabetes. All 10 patients who underwent enucleation were alive and symptom-free as of this writing.

DISCUSSION

Thirty-six patients with a benign mucinous cystadenoma underwent surgical therapy at The Johns Hopkins Hospital

Table 4. FOLLOW-UP

	Resection	Enucleation
Length of stay (days)	10	19.5*
Length of follow-up (mo)	48.6	42.9
Diabetes (%)	10	0
Late deaths (%)	5	0
Recurrence	0	0

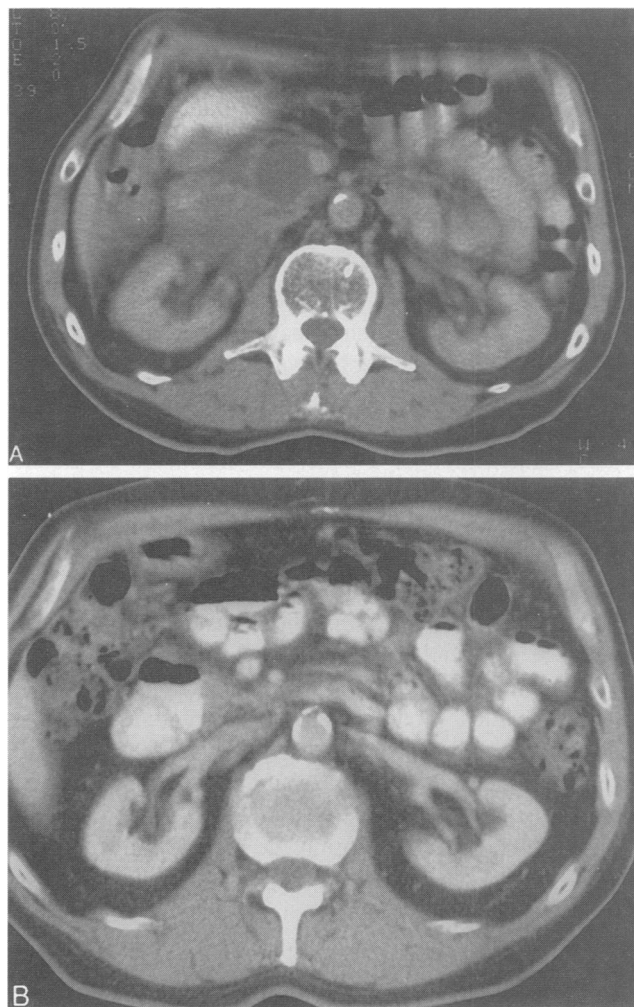* p < 0.02 *vs.* resection by Mann-Whitney rank sum test.

Figure 4. CT of patient (A) before and (B) 7 years after enucleation.

over a 7.5-year period. Ten of these 36 patients (28%) underwent simple operative cyst enucleation rather than resection, which was performed in the other 26 patients. The enucleation group did not differ from the resection group with respect to age, gender, or race. The clinical presentation was also similar, although the patients in the enucleation group were more likely to be asymptomatic and less likely to have abdominal pain. The location of the enucleated cysts removed were head (30%), uncinate (30%), and body or tail (40%). In nine of these patients, resection of pancreatic tissue was avoided by performing enucleation. In the other patient, a coexisting adenocarcinoma in the head of the pancreas was resected using a Whipple procedure, and a benign mucinous cystadenoma was enucleated from the body of the pancreas at the same time. Half the patients in the enucleated group developed a postoperative pancreatic fistula, but the overall morbidity rate did not differ between the two groups. No recurrences were observed in either group. However, late diabetes was observed in 10% of patients, and one late septic death occurred in a patient whose spleen had been removed along with a distal pancreatectomy.

Enucleation of benign tumors is a well-established surgical strategy in the gastrointestinal tract. Hepatic hemangiomas can now be safely removed by enucleation.[3] Hepatic cystadenomas can also be removed by enucleation.[4] Benign gastrointestinal stromal tumors have also been enucleated safely from the esophagus[5] and the stomach.[6] In the pancreas, enucleation has been a successful approach for selected insulinomas,[7] or gastrinomas in the duodenal wall or the pancreas.[8] Most pancreatic surgeons have advocated the resection of cystic tumors of the pancreas, such as mucinous cystadenomas.[9] Enucleation of pancreatic cystic tumors offers the possibility of complete tumor removal without loss of pancreatic parenchyma, possible diabetes, splenectomy, or the anatomic alterations mandated by the Whipple procedure. Enucleation of a pancreatic mucinous cystadenoma,[10] serous cystadenoma,[11] and a solid and papillary neoplasm[12] have all been reported. Advancements in laparoscopic skill and technology now make laparoscopic pancreatic cyst enucleation feasible.[13]

The current report contains the largest series to date of enucleated pancreatic mucinous cystadenomas. This retrospective comparison with pancreatic resection confirms the safety and efficacy of enucleation and provides clues regarding possible improvements for the approach. The high fistula rate suggests that the routine use of prophylactic octreotide might be considered.

Controversy exists regarding the management of cystic lesions of the pancreas, particularly when a presumptive diagnosis of benign cystadenoma is made and the lesion is small. Some have suggested that certain cystic lesions could simply be observed.[14] Diagnostic aspiration of the cyst has also been used to determine the nature of the lesion,[15,16] but others have demonstrated the imprecise nature of preoperative diagnostic modalities in pancreatic cystic lesions.[17] Because of the uncertain nature of cystic tumors of the pancreas and the low reliability of noninvasive tests, many groups have advocated surgical resection.[18,19] Our policy has been abdominal exploration for patients with lesions ≥2 cm in the largest dimension. This policy assumes that the patient is in sufficiently good general health to withstand a major intraperitonal surgical procedure. Exploration is necessary for definitive diagnosis, which requires careful pathologic examination of the entire specimen.

Candidates for enucleation in this series were those with a presumptive diagnosis of benign mucinous cystadenoma of the pancreas. None of these patients were jaundiced or had vascular involvement, and all had small cysts that appeared to be removable by enucleation. The decision to enucleate or to resect must be made in the operating room, based on operative findings. The entire cyst wall must be removable by enucleation. Local invasion or inflammation involving the adjacent pancreas will prevent enucleation. To perform enucleation, the region of the gland approached surgically must be entirely exposed.

This series reveals the advantages and possible disadvantages of the enucleation of benign pancreatic neoplasms.

Intraoperative blood loss is less for enucleation than for resection, and the pancreatic parenchyma is preserved. There were two postoperative deaths in the resection group and none in the enucleation group. However, the incidence of pancreatic fistula was higher in the enucleation group, leading to a longer median hospital stay. Series reporting enucleation for insulinoma also describe pancreatic fistulas.[7,20] Strategies can be used to reduce the incidence of this problem during enucleation. In addition to the use of octreotide, suture of the enucleation bed or Roux-en-Y pancreatojejunostomy might be indicated in selected patients.

Sixty percent of the enucleated lesions were in the head or uncinate *versus* only 27% in the resected group. This difference probably represents the surgeon's aim to avoid a pancreatoduodenectomy for a benign lesion in the head or uncinate process in an otherwise normal pancreas. Seventy-four percent of the distal pancreatectomies in the resection series included splenectomy. Enucleation, had it been feasible, would have prevented splenectomy and its potential long- and short-term complications in these patients. Of course, distal pancreatectomy can be performed without splenectomy, as was accomplished in five of our patients.[21]

This retrospective comparison of resection and enucleation for benign mucinous cystadenomas of the pancreas demonstrates that enucleation is a safe and effective means of surgical extirpation with preservation of pancreatic tissue. As is true for any mucinous cystic neoplasm, an enucleated mucinous cystic neoplasm must be completely sampled for histologic evaluation to rule out small foci of cancer in an otherwise benign-appearing mucinous cystadenoma. The high incidence of pancreatic fistula suggests that additional measures should be taken to avoid this problem, which is usually not life-threatening. Despite the lack of recurrence in this series, careful observation of these patients to determine if they are at greater risk for recurrence years after enucleation will be needed before this procedure can be advocated for widespread use. Nevertheless, we conclude that enucleation is an adequate procedure for benign mucinous cystic neoplasms of the pancreas.

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Discussion

DR. THOMAS R. GADACZ (Augusta, Georgia): Dr. Wells, Dr. Copeland, Members, and Guests. First, I wish to thank the authors for the opportunity to review the manuscript and commend them on a very remarkable series of patients that required not only some difficult preoperative planning but also significant intraoperative judgment.

This remarkable series of 36 patients with mucinous cystadenoma really demonstrate that good results can be achieved with enucleation. I'd like to ask five questions.

Although the fistula rate was 50% in the 10 patients that had enucleation, this did not seem to result in any mortality or, for that matter, significant morbidity. Was there any correlation between the location of the lesion and the incidence of the fistula? That is, were most of the fistulas in the patients who had a cystadenoma in the head of the pancreas?

Second, did any of the patients with enucleation require reoperation for any reason? Although you didn't state that in your manuscript, were there any other problems, particularly with the fistulas?

Third, although you stated that none of the patients that had enucleations turned out to have a cystadenocarcinoma on the final pathology, I think your comment about being somewhat lucky in this regard was very appropriate. In the event that a patient did

have enucleation, say, in the body and you found this out then on permanent section, what would your strategy be in such a patient?

To decrease the incidence of pancreatic fistula, in your manuscript, you mentioned the use of a Roux-en-y applied to the enucleated bed. In what cases would you recommend the use of the roux-en-y?

I wish to thank the Association for the opportunity to comment on this paper. [Applause]

DR. R. SCOTT JONES (Charlottesville, Virginia): Thank you, Dr. Wells, Dr. Copeland.

I wanted to compliment the authors of this study and make a couple of comments. The first is to remind everyone that mucinous cystadenoma of the pancreas is a rare disease, and I would like to point out that in a period of 6.5 years, they accumulated experience of 28 cases total, I believe. And that's a fairly remarkable experience.

Ten of those patients had enucleation. And what this experience does for us is to delineate the variables that we have to consider when making a decision how to treat the lesion. If I could just summarize, it seems to me the things that are important here are the location of the lesion, the size of the lesion, and the surgeon's confidence about whether this is a benign or malignant lesion.

And, very clearly, the ante is fairly high in lesions in the uncinate process in the head of the pancreas, because to resect that is a fairly substantial operation. If you can obtain equally good long-term follow-up with local excision or enucleation, that clearly would be preferable.

Likewise, in the tail of the pancreas, if a lesion can be removed by enucleation and spare the spleen, that, likewise, is an asset. And as we are making this decision, the thing that will linger in our mind about this, and the real tension, will be is this a benign or malignant lesion. And, clearly, if you knew that it was malignant, you would probably prefer to have a margin around the lesion to have the best chance to cure.

Well, we can continue to look at the data here because, in their case, in this series of 10 patients enucleated, they were right every time, and they have had no recurrences, actually, in either group. So I think that the follow-up data that they provided with this excellent study also gives information that will help the surgeon to decide intraoperatively what to do about this.

So I simply want to say that this was an extremely well-written paper, thoughtfully discussed, and I think it is a real bit of new knowledge and insight that will help us to manage patients like this in the future.

Thank you very much. [Applause]

DR. JAMES V. SITZMANN (Washington, D.C.): Thank you, Dr. Wells, Dr. Copeland. I rise to add to the compliments to Dr. Cameron's outstanding pancreas group at Hopkins and to Henry and to Mark and their good work here. It is a stimulating and a challenging set of patients, and I will admit that it is a somewhat controversial series for me. It may be indicative of an example of activities like tightrope walking. It's an example of something that can be done but not necessarily should be done. And so I would rise to raise a couple of questions about the lesion size and the determination by the surgeon to do either resection or enucleation.

In the manuscript that you so kindly provided, you noted there was a difference in the resected ones — about 3.6 cm was the average size, and the enucleated ones were 2.8 cm. Is that to imply that there should be a distinction based on the surgeon at the time